

Table 3.1.1 Summary of Studies on Cataractogenic Effects of Microwave Radiation

Tissue/ Bioeffect	Animal Species	Frequency GHz	Power density kW/m²	SAR W/kg	Time min	Author
Lens/Cataract:						
Posterior cortical	rabbit	2.45	4.2	-	5	Carpenter
		2.45	1.5	138	60	1979
No effect	monkey	2.45	5.0	-	60	Kramar
Cataract	rabbit	2.45	-	100	140	et al 1978
<i>Far field exposure:</i>						
No cataract	rabbit	3.00	5.0	-	30	Appleton
						et al 1975
<i>Cumulative Exposure:</i>						
Cataract	rabbit	2.45	1.2	-	60 (x 24)	Carpenter
						1979
Cataract	rabbit	2.45	1.8	-	60 (x20)	Carpenter
						et al 1974
Cataract	rabbit	2.45	1.5	-	60 (x32)	Carpenter
						1979
No cataract	rabbit	2.45	0.1	17	552 (x180)	Guy et al
						1980
No Cataract	monkey	9.30	1.5	-	15x40 (10 h total)	McAfee
						et al 1979

At frequencies above 10 GHz, penetration decreases and power absorption is increasingly restricted to the superficial tissue. At 915 MHz the estimated distribution of SAR (Guy et al 1974) in the eyes of rabbits gave the peak SAR as 25% lower than that resulting from exposure at 2.45 GHz. The maximal SAR was found to occur in the rabbit brain, being 36% higher than in the eye. It is likely that other biological endpoints will become limiting factors before exposure is sufficient to induce cataracts. At higher frequencies of 35 and 107 GHz effects of acute exposure were limited to the cornea of rabbit eyes (Rosenthal et al 1976).

Whole-body exposure to far-field radiation, which is relevant to many occupational situations, has not been reliably associated with experimental cataract induction. The lenses of anaesthetised rabbits exposed in the far-field to 3 GHz for 15-30 min at 5 kW/m² were unchanged. Cataracts were not found in macaque monkeys trained to expose their faces to 9.3 GHz radiation at 1.5 kW/m² for a total exposure period of up to about 10 h over 3 months (McAfee et al 1979). In a study of the cumulative effects (table 3.1.1) of repeated sub-threshold exposure of anaesthetised rabbits to 2.45 GHz radiation, the lowest power density capable of producing cataracts was 1.2 kW/m² for 1 h, repeated 20-24 times (Carpenter 1979).

3.1.2 Corneal Lesions

In addition to lens opacity, corneal endothelial lesions were produced in the eyes of anaesthetised monkeys exposed to continuous or pulsed wave (10 μ s pulses repeated at 100 pulses per second) 2.45 GHz radiation (Kues et al 1985) (Table 3.1.2). Pulsed radiation produced endothelial lesions after a single 4 h exposure to 100 W/m² where the average SAR in the anterior chamber of the eye was estimated *in vivo* as 2.6 W/kg. Body temperatures dropped during exposure by about 2.5°C in both sham-exposed and exposed monkeys due to the anaesthesia. When the exposure was increased to 4 h on three consecutive days, there was increased vascular leakage from the iris blood vessels into the aqueous humour (Kues et al 1988). When the eyes were pretreated with the ophthalmic drug timolol maleate used in the treatment of glaucoma, the leakage was increased at power densities as low as 10 W/m² where the local SAR was estimated at 0.26 W/kg (Monahan et al 1988).

Table 3.1.2 Summary of Ocular Effects from Low Level Microwave Radiation

Tissue/ Bioeffect	Animal Species	Frequency GHz	Power density kW/m ²	SAR W/kg	Time min	Author
Cornea:						
<i>Corneal lesions</i>	rabbits	35	0.4		60	Rosenthal et al 1976
transient - lesion appear after 24h		107	0.4		60	
Endothelial lesions	monkey	2.45	0.1	2.6	240	Kues et al 1985
		2.45(pls, cw)	0.3	-	-	
Corneal lesions	monkey	2.45(pls)	0.1	2.6	240 x 3	Kues et al 1988, 1992
Iris:						
<i>Extravasation of blood vessels</i>	monkey	2.45(cw)	0.2	6.3	240 x 3	Kues et al 1988, 1992
Extravasation increased (+ glaucoma drug)	monkey	2.45(pls)	0.01	0.26	240 x 3	
No effect	monkey	2.45	0.002	-	240 x 3	" "
Retina:						
<i>Retina degeneration</i> (long term 10 weeks)	monkey	2.45	0.05	-	240 x 3	Kues et al 1990
Retina vacuolation and detachment (+ glaucoma drug)	monkey	2.45	0.10	-		Kues et al 1990
Retina degeneration	monkey (unanaes- thetised)	1.25 (pls) [16 pps]		4.0	240 x 3 (x 1-10)	Kues et al 1994
Electro-Retino-Gram depressed		2.45 (pls) [100 pps]		2.6		

Damage to the retina has since been reported (Kues et al 1990) following exposure to pulsed 2.45 GHz radiation at 50 W/m² for 10 weeks. When exposure to 100 W/m² followed timolol maleate treatment extensive vacuolation of the outer retinal layers was observed together with focal retinal detachment. The effects were produced when microwave radiation immediately followed the application of a single drop of the ophthalmic drug timolol maleate (0.5%) or pilocarpine (2%). When combined with either drug the power density threshold was reduced by an order of magnitude (from 10 to 1 mW/cm²) for the induction of corneal endothelial lesions and increased vascular permeability of the iris (Kues et al 1992). Sodium fluorescein iris angiography was used to diagnose vascular integrity. Positive results were also obtained using the glycoprotein horseradish peroxidase showing that microwave exposure resulted in diffusion of large molecules (40,000 molecular weight, and 100 times larger than sodium fluorescein) out of the iris blood vessels.

In the latest addition to this work on ocular lesions from low SARs, Kues et al (1994) reported cytological damage in retinal neuroepithelium under various exposure conditions, when monkeys were chair-restrained. The effect is considered to be permanent as it is still apparent at one year post-irradiation. Using frequencies of 1.25, 2.45 and 2.85 GHz, they reported effects at 4 W/kg SAR that were related to the shape of the pulse and the ratio of peak power to pulse length rather than to the SAR value. When applied using rapid rise-time square pulses, the effects were demonstrated by histology and depressed electroretinogram. The cellular changes reported include cytoplasmic vacuolation and disrupted plasma membrane. The mechanism is uncertain. At a frequency of 2.45 GHz, and 10 μ s pulses repeated at 100 Hz, the effects were observed at a SAR of 2.6 W/kg (average value in the eye, i.e., not whole-body average).

It has been proposed that the action of free radicals may be involved in the breakdown of the ocular membranes leading to extravasation. Oxygen radicals are known to increase vascular permeability (Hull 1985) in the rabbit iris. As both timolol and pilocarpine are known to bind to ocular melanin, and microwave interaction with melanin generates free radicals, a potential mechanism exists. It needs to be established if free radicals can be released by the low energy levels causing vascular leakage in these animal experiments.

3.2 HAEMATOLOGY AND IMMUNOLOGY

SUMMARY

The literature contains reports of a large number of studies on the effects of microwave and RF radiation on the haematopoietic system and on immune responses. These have been well reviewed (Roberts 1983; Smialowicz 1984; NCRP 1986; Szmigielski et al 1988; NRPB 1992; WHO 1993). The conflicting nature of many early reports makes interpretation difficult and although later studies have been improved with more rigorous experimental design and improvement in dosimetry, the overall effects of microwave and RF exposure are still not well understood. There is good evidence that receptor sites on cell membranes are sensitive to EMR and, therefore, some effects on the sensitive immunological system may be expected. Many of the effects are transient. Contradictory effects have been reported in rodents.

Various components of the immune system have been affected by microwave exposures. Interpretation may be confounded by the complex nature of immune responses, which can involve changes in the numbers of circulating lymphocytes and leucocytes, and the sensitivity of the system to minor changes in temperature. Consistent effects on the haematopoietic and immune systems are mostly associated with thermal stress, although the occasional report appears at SAR levels too low to induce significant amounts of heating. A recent report of stimulated immune response in male rats exposed to low level (0.14 W/kg) microwave radiation is contrary to expectations. Difficulties in interpretation are exacerbated by the experimental constraints of making isolated observations within a complicated sequence of changes.

This problem is common to much of the research carried out on cellular RF responses. Separate research groups generally study a small part of a chain of events. Species difference is a further variable that complicates these issues.

Introduction

The lymphocyte population consists of B-lymphocytes, the precursors of plasma cells or antibody secreting cells, and T-lymphocytes required to express cellular immune responses including delayed hypersensitivity, cell-mediated cytotoxicity and helper cell function. Experiments have been studied on the mitogen responses of B- and T- lymphocytes, the number of B- lymphocytes bearing

complement receptors, natural killer cell (a T-lymphocyte sub-group) activity and the antibody response of B-lymphocytes. Lymphocytes from exposed animals have been studied by way of their *in vitro* response to mitogens (agents that stimulate transformation to lymphoblasts and mitotic division). Thus, the functional integrity of the cell and the relative frequencies of B- and T- cells can be evaluated by using B- and T- specific mitogens.

Experimental Evidence

3.2.1 Haematopoietic System

Early studies measured peripheral blood cell concentrations and reported an increase in erythrocyte and neutrophil counts but a reduction in total leucocyte and lymphocyte counts in rats exposed to pulsed 24 GHz microwave radiation at 100 W/m² for 18 h or 200 W/m² for 7.5 h. The SARs were estimated to be 1.5 and 3 W/kg, respectively (Smialowicz 1984). These experiments are typical of many early studies that are complicated by the lack of appropriate sham-exposed controls and absence of interpretation of the biological significance of the effect.

Heating is often involved in haematological responses to microwave and RF radiation. A reported decrease in peripheral lymphocyte count and increase in neutrophil count (Liburdy 1977) was observed in mice exposed to 26 MHz at a SAR of 13 W/kg, which raised the rectal temperature by 2 - 4°C (Table 3.2.1). The response was greatest after 3 h exposure. In contrast, exposures that were not accompanied by a detectable increase in body temperature have reported absence of effects.

A lack of effect on peripheral blood count in mice exposed to 2.45 GHz was reported where the SAR was estimated at 22 W/kg (Smialowicz et al 1979 a). Peripheral blood cell count was unchanged in rats, in the absence of a measurable rise in whole body temperature, following exposure for; (a) 1 h per day for 90 days to 2.4 GHz at 50 W/m² (SAR estimated at 1 W/kg) (Djordjevic et al 1977), (b) 22 h per day for 70 consecutive days to 970 MHz at a SAR of 2.5 W/kg (Smialowicz et al 1981a), or (c) for 8 h to 2.45 GHz at SAR 0.44 to 2.2 W/kg (Galvin et al 1982). See table 3.2.1.

Table 3.2.1 **Summary of Reported Effects of Electromagnetic Radiation on the Haematopoietic System**

Exposure conditions	Effect	Reference
24 GHz 100 W/m ² , SAR= 1.5 W/kg, 18 h 200 W/m ² , SAR=3.0 W/kg, 7.5 h	Rats: Increased neutrophil count Decreased lymphocyte count Rectal temperature increased = 1°C	Deichmann et al 1959, 1964
26 MHz (cw) SAR=13 W/kg up to 3 h	Mice: Increased peripheral neutrophil count Decreased lymphocyte count Rectal temperature increased 2-4°C	Liburdy 1977
2.4 GHz (cw) 50 W/m ² , SAR = 1 W/kg 1 h per day x 90 days	Rats: No effect on peripheral blood cell count	Djordjevic et al 1973, 1977
100 W/m ² , SAR = 2 W/kg 2 h per day x 30 days	Increased erythrocyte count Rectal temperature increased 1°C	
970 MHz (cw) SAR=2.5 W/kg 22h per day x 70 days	Rats: No effect on blood count No reported temperature increase	Smialowicz et al 1981 (a)
2.45 GHz (cw) 300 W/m ² , SAR=2.2 W/kg 0.5 h per day x 16 days	Rats: No effect on peripheral blood count No measured temperature increase	Galvin et al 1982

**Table 3.2.1 Summary of Reported Effects of Electromagnetic Radiation
on the Haematopoietic System**

Exposure conditions	Effect	Reference
2.45 GHz (cw) SAR= 1-5 W/kg	Rats: No consistent changes in erythrocyte, or leucocyte counts following prenatal and postnatal exposure	Smialowicz et al 1979 (b)
425 MHz (cw) SAR=3-7 W/kg	Increased lymphocyte response to T- and B- mitogens	Smialowicz et al 1982
100 MHz (cw) SAR=2-3 W/kg, 4 h per day	No effect on blood cell count or antibody response	Smialowicz et al 1981 (b)
3 GHz (cw & pulsed) 35 W/m ² , SAR = 0.5 W/kg 3 h per day x 90 days	Guinea pigs and rabbits: Abnormal nuclei, depressed mitosis in bone marrow cells Rectal temperature unchanged	Baranski et al 1971
2.45 GHz (cw) 150 W/m ² , SAR=11 W/kg 0.5 h per day x 9 days	Mouse bone marrow: Reduced ability to form myeloid or erythroid colonies <i>in vitro</i>	Huang & Mold 1980
2.88 GHz (pulsed) SAR=4.5 W/kg up to 360 days	Mice: Inconsistent results on cloning efficiency of myeloid cells	Ragan et al 1983
2.45 GHz (cw) 300 W/m ² , SAR=22 W/kg 0.5 h per day x 22 days	Mice: No effect on peripheral blood count No measured temperature increase	Smialowicz et al 1979 (a)

Substantial abnormalities in haematopoietic development in bone marrow cells have been reported in guinea pigs following a single exposure to 3 to 4°C hyperthermia for 60 min (Edwards & Penny 1985). Similar significant changes in nuclear development were observed following a temperature increase of only 2.5°C for 6 mins when produced by localised absorption of pulsed ultrasound (Barnett et al 1991) in a single acute exposure.

A review of early studies (Smialowicz 1984) reported a lack of consistent effect of microwave or RF exposure on peripheral blood cells in developing rats. Studies by the same author (Table 3.2.1) also reported no consistent changes in erythrocyte, leucocyte or differential leucocyte cell count in rats exposed prenatally and postnatally (for up to 41 days) over a range of frequencies; 100 MHz radiation at SAR 2-3 W/kg (Smialowicz et al 1981 b); 425 MHz radiation at 3-7 W/kg (Smialowicz et al 1982); and 2.45 GHz radiation at 1-5 W/kg (Smialowicz et al 1979 b).

The apparent trend of a temperature-related effect has doubtlessly contributed to the notions, commonly expressed, that if the energy deposition from EMR does not heat it cannot hurt. This rather simplistic approach is only acceptable for gross effects. The subtleties of cell membrane responses requires an understanding and development of other non-thermal mechanisms.

Studies on the effects of microwave exposure on haemopoietic tissue in bone marrow revealed abnormalities in nuclear structure and depressed mitosis (Baranski 1971) in guinea-pigs and rabbits exposed to pulsed or continuous wave 3 GHz microwave radiation at 35 W/m² for 3 h per day over a period of 3 months. The SAR was estimated to be 0.5 W/kg and rectal temperatures were unchanged.

Studies to evaluate the effects of low level exposure on the haemopoietic stem cells using *in vitro* colony forming assays have been inconsistent. Huang and Mold (1980) exposed mice to 2.45 GHz radiation at 150 W/m² (SAR 11 W/kg) for 30 min per day for 9 days and reported a reduction in the ability of bone marrow cells to form myeloid and erythroid colonies. Rectal temperature was variable, but not significantly increased. An inconsistent lack of effect on cloning efficiency of myeloid stem cells from mice exposed for up to 360 h to 2.88 GHz pulsed microwaves at SARs up to 4.5 W/kg was reported (Ragan et al 1983). In a review Smialowicz (1984) suggested that there is a marked difference in the

kinetic response of the haematopoietic system to heat stress from microwave-induced heating and conventional heating. Radiation at 2.45 GHz frequency is quite penetrating (in small animals) and is likely to have set up temperature gradients within the mouse different to those set up by external heating, even though rectal temperatures were similar.

3.2.2 *Immune System*

A single study on rhesus monkeys reported enhanced mitogen response in lymphocytes after 30 min exposure to 10.5, 19.27 or 26.6 MHz radiation at SARs between 0.4 and 2.0 W/kg (Prince et al 1972). Rectal temperatures were reported to be increased by 2.5°C at the higher level of exposure.

Contradictory results have been reported using the appearance of a surface marker (complement-receptor) specific to a stage in the maturation of B-lymphocytes, following microwave radiation. One group of workers (Wiktor-Jedrzejczak et al 1977, 1980) reported an increase in the number of complement-receptor positive lymphocytes and an increase in B- cell mitogen response following exposure to 2.45 GHz radiation at 15 W/kg for 30 min. The effect was thought to be due to stimulation of B- cells into early maturation. Independent duplication of the study found a similar result only when the exposure level was raised to 28 W/kg resulting in a level of thermal stress that killed some mice (Smialowicz et al 1981 c) (See Table 3.2.2).

There is a suggestion that differences in results may be due to differences in mice strain specificity as Schlagel et al (1980, 1982) reported a negative effect in Balb/C mice and an increase in complement-receptor lymphocytes in CBA/J mice. It has been suggested that the difference in response between the two strains may be due to the presence of a single gene (Schlagel et al 1982; WHO 1993). An important experimental variable that has not been adequately investigated is that of the environmental conditions associated with each of the exposures. Differences in air flow, humidity and ambient temperature may significantly alter the levels of thermal stress for a given level of microwave exposure.

Liburdy (1980, 1987) has examined the central role of thermal stress in the effect of microwaves on the immune system. Mice were exposed or sham-exposed for 15 min (single or repeated exposures) to 26 MHz radiation at 5.6 W/kg or to warm air to induce an increase in core temperature of 2-3°C. A number of effects were observed when the RF-treated mice were compared with either the sham-exposed or the heat-treated animals. A transient reduction in peripheral

**Table 3.2.2 Summary of Reported Effects of Microwave Irradiation
on the Immune System**

Exposure conditions	Effect	Reference
10.5, 19.27, 26.6 MHz (cw) SAR = 0.4 - 2.0 W/kg 0.5 h	Rhesus monkeys: Enhanced mitogen response Rectal temperature increased by 2.5°C at 2 W/kg	Prince et al 1972
2.45 GHz (cw) SAR to 21 W/kg 0.25 h per day x 5 days	Chinese hamsters: Transient increase in rate of transformation of unstimulated peripheral blood lymphocytes (to lymphoblasts) Decreased frequency of mitosis in mitogen-stimulated lymphocytes	Huang et al 1977
2.45 GHz (cw) 150 W/m ² SAR to 11 W/kg 0.5 h per day x 17 days	Balb/C mice: Fluctuating changes in mitogen response to T- and B-lymphocytes	Huang & Mold 1980
2.45 GHz (cw) 300 W/m ² SAR = 22 W/kg 0.5 h per day x 22 days	Balb/c mice: No effect on mitogen response of T- and B-lymphocytes	Smialowicz et al 1979 (a)
2.45 GHz (cw) SAR to 21 W/kg 1.5 h per day x 9 days	CBA/J mice: No effect on T- and B-cell mitogen response	Smialowicz et al 1983
2.45 GHz (cw) SAR to 15 W/kg 0.5 h	CBA/J mice: Increased number of lymphocytes with complement receptor marker Increased mitogen response	Wiktor- Jedrzejczak et al 1977, 1980

**Table 3.2.2 Summary of Reported Effects of Microwave Irradiation
on the Immune System**

Exposure conditions	Effect	Reference
2.45 GHz (cw) SAR = 28 W/kg	CBA/J mice: Increase in complement-receptor positive lymphocytes	Smialowicz et al 1981 (c)
2.45 GHz (cw) SAR = 14 W/kg	CBA/J mice: Increase in complement-receptor positive lymphocytes	Schlagel et al 1980, 1982
2.45 GHz (cw) SAR = 14 W/kg	Balb/c mice: No effect on number of complement- receptor positive lymphocytes	
2.45 GHz (cw) SAR to 22 W/kg 0.5 h per day x 22 days	Balb/c mice: No increase in complement-receptor positive lymphocytes	Smialowicz et al 1979 (a)
2.45 GHz (cw) SAR = 13 W/kg 1 h	Hamsters: Activation of macrophages for up to 15 days post-exposure Rectal temperature increased by 2°C	Rama Rae et al 1983
2.45 GHz (cw) SAR = 13 W/kg 1 h SAR = 8 W/kg 1 h	Hamsters: Transient decrease in natural killer cell activity of T-lymphocytes Colon temperature increased 3-3.5°C No effect of natural killer cell activity	Yang et al 1983

**Table 3.2.2 Summary of Reported Effects of Microwave Irradiation
on the Immune System**

Exposure conditions	Effect	Reference
2.45 GHz (cw) SAR = 21 W/kg 1.5 h	Mice: Transient decreased in natural killer T-cell activity Increased macrophage activity Significant temperature increase	Smialowicz et al 1983
2.45 GHz (cw) SAR = 11 W/kg 0.5 h per day x 9 days	Mice: No change in Natural Killer cell response Increased activation of macrophages No increase in rectal temperature	Huang & Mold 1980
2.6 GHz (cw) SAR = 3.8 W/kg 0.5 h SAR = 19 W/kg 0.5 h	Mice: No change in distribution of radio-labeled splenic lymphocytes Altered distribution of lymphocytes in lung, spleen and bone marrow	Liburdy 1980
Warm air to elevate rectal temperature by 2°C	No change in distribution of lymphocytes	
26 MHz (cw) SAR = 5.6 W/kg 0.25 h single or repeated exposure	Mice: Transient reduction in peripheral lymphocytes & increase in neutrophils compared to heat-treatment of 2-3°C Increased levels of T- and B-lymphocytes & plasma corticosteroids	Liburdy 1987

lymphocytes and an increase in numbers of neutrophils occurred, which could be sustained by multiple exposures. RF exposure also resulted in an increase in T- and B-lymphocytes in the spleen and elevated plasma corticosteroid levels. In addition, the ability of mice to develop a delayed hypersensitivity (to sheep red blood cells) was suppressed by the RF exposure.

The effect of RF exposure and elevated temperature was also determined on lymphocyte migration (Liburdy 1980). This was measured by the activity of radio-labelled splenic lymphocytes in mice exposed for 1 h to 2.6 GHz radiation at 3.8 W/kg. This was compared with exposure to 19 W/kg or to warm air, both of which were sufficient to raise rectal temperatures by 2°C. Exposure at 19 W/kg caused a significant alteration in the distribution of lymphocytes between the lung, spleen and bone marrow, whereas exposures to 3.8 W/kg or warm air did not produce these changes.

Liburdy suggested that whole-body RF or microwave exposure induces heat stress which activates the hypothalamic-hypophyseal-adrenal complex to release adrenal steroids into the blood, leading to the transient changes in blood cell counts and other haematopoietic and immunologic changes associated with RF or microwave exposure. The difference in response to exposures with warm air and microwave radiation is probably due to differences in energy deposition. Microwave-induced heating works by a different mechanism by being more rapid, and will have acted as a thermal stress for longer than warm air in a given exposure.

Exposure to thermogenic levels of microwave radiation has also been shown to cause changes in macrophage and natural killer cell (NK) activity, implicated for example in tumour cell cytotoxicity (Table 3.2.2). Activation of macrophages and some transient decrease in the NK activity of T- lymphocytes was reported after exposure to 2.45 GHz radiation (Table 3.2.2). Since colonic temperature (and plasma corticosteroids) was appreciably elevated at the higher level of exposure, the decreased activity is probably due to heat stress.

The latest reported effects from a group in Hungary (Elekes et al 1994) adds a further degree of uncertainty to the subject. The data was presented at the BEMS conference and, therefore, has not yet been peer-reviewed, but a paper has been submitted for publication (for this reason the data is not included in the table 3.2.2). In their study Balb/C mice were exposed to 2.45 GHz, cw or 50 Hz amplitude modulated, at SAR 0.14 W/kg. Exposures of different durations were

applied for six consecutive days and mice were injected with sheep red blood cells on the second day of exposure. The number of antibody producing cells in the spleen of male mice was significantly increased with daily 3 h exposures. Exposures for longer durations had less of an effect. Female mice were unaffected. No logical explanation was given for the observed result. The authors have experience in ionizing radiation biology and have recently turned their attention to EMR.

3.3 TERATOGENIC EFFECTS

SUMMARY

It is well understood that a moderate elevation of body temperature during embryonic/fetal development is teratogenic in many animal species (Warkany 1986) and in humans (WFUMB 1992; Edwards 1986, 1993). Data from whole-body heating of pregnant animals in environmental chambers, indicates a threshold of 2.5°C above basal physiological temperature for the development of major abnormalities in the central nervous system (Germaine et al 1985). The type and magnitude of effect depends on the gestation stage and extent of the thermal insult.

Thus, exposures to microwave or RF radiation that will induce significant rises (>1.5°C) in maternal body temperature would be expected to result in teratogenic effects. Most of the literature reports effects of exposure to substantial levels of SAR and the associated adverse developmental effects are consistent with RF-induced hyperthermia. These are gross effects that are easily detected.

More sensitive, and potentially important, disturbance of CNS function has not been adequately investigated, particularly where offspring may appear normal. Research in this area is recommended.

Most of the work has been clearly focused on the safety issues relating to microwave ovens at 2.45 GHz frequency. It is tempting to assume that teratogenesis will only be produced when the RF radiation is sufficient to significantly raise the embryonic or fetal temperature. However, recent reports from a single laboratory have claimed delayed development in chick embryos exposed to 428 MHz at 5.5 mW/cm² which they consider to be a non-thermal effect.

Similarly, a report by an apparently respectable research group (Tofani et al 1986) of significant effects on postimplantation survival and cranial ossification in rat fetuses following chronic exposure to very low level RF radiation cannot be explained by the accepted thermal mechanism (Table 3.3.1). Data that is relevant to exposures at telecommunications frequencies, particularly for cellular telephones, is urgently needed.

Introduction

Cells are most sensitive to damage by physical agents, such as heat, during the process of cell division. If mitosis in neurons is arrested by a transient temperature increase during embryonic development the resulting neural deficit may not be restored, although the fetus may continue to develop and appear morphologically normal (Edwards et al 1974). There are critical periods during gestation when the embryo is more susceptible to teratogenic effects. At the time of formation of the neural plate and closure of the neural tube interactions can result in severe neural tube defects, retarded brain development, exencephaly, and microphthalmia. Other effects have been reported following a single brief exposure to an increase in temperature of 3.5°C (Cuff et al 1993).

These gross effects are readily detected. However, low level interference that delays development of the cerebral cortex or impairs neural migration at later stages (around 22 weeks human gestation) is far more difficult to detect. The resulting impairment of neurological function may create learning difficulties. Non-deforming retardation of brain growth with reduced learning performance is the most common abnormality found in offspring from heat-exposed guinea pigs (Edwards 1968). The literature on teratogenic effects of electromagnetic radiation does not address this more sensitive issue.

3.3.1 Experimental Evidence

Exposure to high levels of RF will induce significant rises in the temperature of the mother and embryo. The resulting hyperthermia will bring about abnormal development both by direct interaction on the embryo and fetus and indirectly through compromised maternal physiology. Such an effect has been demonstrated where absorbed ultrasonic energy produced maternal hyperthermia (Barnett & Williams 1990). The teratogenic nature of hyperthermia is now widely accepted (Edwards 1993).

Although many of the studies on RF- induced teratogenicity applied repeated exposures this would add little value to the results if the effect was due entirely to a thermal mechanism. For the type of abnormalities reported, there is no reason to assume that repeated exposures at subthreshold levels would be any more effective than a single exposure to heat. In fact, the bioeffects data base on hyperthermia consists primarily of results from a single exposure to heat usually at a predetermined critical stage of neural development.

Table 3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiation

Exposure conditions	Effect	Reference
27.12 MHz (cw diathermy) SAR = 11 W/kg until colonic temperature reached 43°C (20-40 min) Acute exposure at one of 8 different stages of gestation	Rats: Embryonic and fetal death Reduced fetal weight and size Skeletal and visceral abnormalities Brain, facial and ophthalmic abnormalities Type of malformation relates to gestation stage of exposure Rectal temperature increased by 4.5°C	Lary et al 1982
27.12 MHz (cw) SAR = 11 W/kg Exposed until colonic temperature reached specific values in the range 41-43°C (10-40 min) Irradiated on day 9 (neural fold stage) of gestation	Rats: Malformations including anophthalmia, microphthalmia, exencephaly, encephalocoele, abnormal cranial skeleton Prenatal death Reduced fetal weight and size Temperature threshold 41.5°C (increase of 3°C) for 10-40 min	Lary et al 1986
27.12 MHz (cw) 1 W/m ² SAR = 0.0001 W/kg Exposed throughout gestation (day 0 to 20)	Rats: Decreased post-implantation survival Reduced cranial ossification No significant change in rectal temperature	Tofani et al 1986
100 MHz (cw) SAR = 0.4 W/kg 6.6 h per day on days 6 to 11 of gestation	Rats: No teratogenic or embryotoxic effect	Lary et al 1983 (b)

Table 3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiation

Exposure conditions	Effect	Reference
915 MHz (cw) 10 W/m ² SAR = 3.5 W/kg 6 h per day throughout gestation	Rats: No fetal anatomical defects No behavioural changes Maternal rectal temperature not elevated	Jensh et al 1982 (a,b)
2.45 GHz (cw) 20 W/m ² SAR = 2-4 W/kg 6 h per day throughout gestation	Rats: No significant increase in abnormalities No significant alterations in neonatal reflex tests or adult behavioural tests Increased activity levels in exposed offspring No increased rectal temperature in dams	Jensh et al 1983 (a,b)
2.45 GHz (pulsed 8µs, 830 pps) 5 W/m ² SAR = 0.4 W/kg from day 2 to 18 of gestation	Rats: No effect on brain development, weight, RNA and DNA content	Merritt et al 1984
2.45 GHz (cw) SAR 6 W/kg 1.6 h per day on days 6 to 15 of gestation	Rats: Decreased fetal body weight associated with immature skeletal development Reduced sternal ossification Maternal temperature increased by 1.5°C above normal	Berman & Carter 1984

In reviews of the teratogenic effects of RF exposure (O'Connor 1980, 1990) the effects commonly described for rodents (CNS abnormalities including exencephaly, reduced fetal weight, and increased fetal resorptions) are typical of those induced by a single exposure to whole body hyperthermia.

The reported abnormalities and deaths (Lary et al 1982) in rats exposed to 11 W/kg at 27.12 MHz were associated with elevated rectal temperature to 43°C in the dam (Table 3.3.1.). This represents an increase of 4.5°C above the basal temperature for rats and exceeds the threshold temperature level for such abnormalities (Walsh et al 1985; Germaine et al 1985; NCRP 1992; WFUMB 1992). However, later experiments by the same author found the threshold temperature for a 40 min. exposure to be 41.5°C (ΔT 3°C).

Teratogenic effects of RF radiation have been demonstrated in both rats and mice, although usually at higher SARs in the latter animal species. There is no evidence from hyperthermic studies to suggest different teratological effects in species although some animals such as rats may be more likely to abort. Different effects are most likely to be a function of body dimension relative to the RF field and relative efficiencies in dissipating body heat.

In fact, the results of studies on the thermal effects of RF radiation in species of different body mass (Gordon & Ferguson 1984; Gordon 1988) show that substantially greater dose rate is required to raise the body temperature in smaller animals. The SAR required to increase body temperature by 1°C in a 0.3 kg mouse is approximately 40 times greater than that required for a 3 kg rabbit. This being the case, one might question the value of using small animals such as mice to extrapolate biological effects to humans where the relative body mass could result in differences in absorbed dose by factors of 3 orders of magnitude. The data derived from mice would, thus, substantially underestimate an anticipated thermal effect in humans.

There have been a number of reviews of the literature on hyperthermia and RF teratology literature that agree on a reliable association between the magnitude and duration of heating and the consequent bioeffect. Berman (1984) and Berman et al (1984) concluded that malformations and prenatal death occur when the core temperature of RF-exposed dams exceeds 40°C. At lower temperatures the primary effect is decreased fetal or neonatal weight. The results of a dose-response study by Lary et al (1986) support this view (Table 3.1.1).

Table 3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiation

Exposure conditions	Effect	Reference
6 GHz (cw) SAR = 7 W/kg 8 h per day throughout gestation	Rats: Retarded fetal growth Learning difficulties in female offspring No structural abnormalities No significant change in maternal rectal temperature	Jensh 1984 (a,b)
2.45 GHz (cw) 28 W/m ² SAR = 16.5 W/kg 1.6 h per day on days 6 to 17 of gestation	Mice: Reduced body weight Significantly low brain weight Persistent delay in postnatal brain development No change in postnatal maturation of skeleton No increase in maternal rectal temperature	Berman et al 1984
2.45 GHz (cw) 40 W/m ² SAR = 16-18 W/kg 2 h per day x 7 days	Mice: Significant inhibition of embryonic growth Increased number of resorptions Intracranial bleeding Significant decrease in postimplantation survival Increased rectal temperature of dam 1.5 - 2°C	Chazan et al 1983
10 mW/m ² SAR = 4-5 W/g 2 h per day x 7 days	No teratogenic effects No increase in maternal temperature	Chazan et al 1983

Table 3.3.1 Summary of Teratogenic Effects of RadioFrequency Radiation

Exposure conditions	Effect	Reference
2.45 GHz (cw) 10 W/m ² SAR = 0.5 W/kg 100 W/m ² SAR = 5 W/kg 400 W/m ² SAR = 18 W/kg 2 h per day from day 1 to 18 of gestation Cytosine arabinocide (10mg/kg) given on day 9	Mice: No effect Reduced fetal weight Increased post-implantation deaths Reduced fetal weight Maternal rectal temperature increased by 2°C Cleft lips and palate Incidence of abnormality enhanced by all above RF exposures compared to effect of drug alone	Marcickiewicz et al 1986 Marcickiewicz et al 1986
2.45 GHz (cw) 5 mW/cm ² SAR = 7 W/kg 4 h twice per day on days of gestation 1 to 15	Mice: Reduced maternal weight gain and fetal weight in irradiated and sham- irradiated compared to cage controls	Nawrot et al 1981
21 W/m ² SAR = 28 W/kg 4 h twice per day on days 1 to 6 on days 6-15 of gestation	Significant decrease in maternal weight gain Increased maternal colonic temperature by 1°C	Nawrot et al 1981
30 W/m ² SAR = 40 W/kg 4 h twice per day on days 1-6 (pre-implantation) 4 h twice per day on days 6-15 pre- and post-organogenesis	Significant decrease in implantation sites, and reduced fetal weight Increased maternal colonic temperature by 2.3°C Significant increase in malformations, cleft palate	Nawrot et al 1981

The temperature threshold for gross anatomical malformations and prenatal death in rats was 41.5°C (being 3°C above their normal body temperature).

Nawrot et al (1981) exposed pregnant mice at stages pre-and-post-organogenesis to a range of microwave power and reported fetal abnormalities including cleft palate that are commonly associated with hyperthermia. They stated that exposures to power densities of 21 or 30 mW/cm² (SARs 28 and 40 W/kg, respectively) elevated maternal colonic temperature by 1 or 2.3°C. The exposure regimen of 8h per day repeated daily for seven days is far beyond that required to induce the reported effects by heat alone. A single exposure to ambient temperature increase above 2°C for 1 hour is sufficient to produce such effects in a range of animal species (Edwards 1993). The authors also reported that the normal rate of maternal weight gain during pregnancy was depressed when the maternal temperature increased by 1°C. This is clear evidence that maternal physiology was compromised by the severe exposure conditions. Similar effects from maternal physiological compromise were reported in a study into the mechanism responsible for ultrasound-induced fetal weight reduction in mice (Barnett & Williams 1990). These effects were produced under conditions in a single exposure that avoided temperature increase at the fetus.

A review by Lary and Conover (1987) describes studies by two groups where the body temperature of rats was lowered prior to exposure to 27 and 2450 MHz radiation. Intensity levels that normally induced abnormalities produced no effect in hypothermic rats indicating that the mechanism for effects was thermal and not due to field-specific effects.

There have, however, also been some reports of teratogenic effects of RF radiation that are inconsistent with a thermal mechanism. Tofani et al (1986) reported significant development perturbation in rat fetuses following exposure throughout gestation (20 days) to extraordinarily low SAR of 0.1 mW/kg. Saito et al (1991) reported retarded development and embryonic death in chick embryos exposed to 428 MHz, SAR 5.5 mW/kg throughout most (20 days) of the incubation period. Saito et al (1986, 1987) also reported retarded development and reduction in thymus weight in newborn mice following exposure to 433 and 906 MHz at similarly low levels. As the papers are written in Japanese it is impossible to give any further details or comment on the content. Results of another author (Jensh 1984 a, b) that do not fit the accepted scheme of temperature-based teratogenic effects are from chronic exposures. Rats were exposed for 8 h per day throughout pregnancy to 6 GHz at SAR of approximately

7 W/kg. While rectal temperature was reported to be unchanged, the fetuses showed growth retardation. There was no evidence of structural abnormalities but female offspring exhibited impaired learning ability and males showed increased activity levels (Table 3.3.1). The validity of dam's rectal temperature as a measure of RF teratogenesis is questioned.

Several investigators have reported significant physiological and behavioural changes in animals prenatally exposed to RF fields which produced little or no increase in body temperature, while others have reported no effects at these levels. Of the positive-effect reports, decreased fetal or postnatal body weight was most commonly reported. This effect may be due to: (1) highly non-uniform absorption of RF energy producing localised appreciable levels of heating in the uterus or fetal or maternal organs, or (2) due to a non-specific stress response.

A commonly reported effect associated with low level interactions with various physical or chemical agents is that of apparent growth retardation, usually detected as low birth weight. Such effects have been reported in the teratogenesis literature, and described as a fetal stress response. The effect has been reported following exposure to low intensity ultrasound where insignificant bulk heating was involved (Barnett et al 1990; Tarantal and Hendrickx 1989).

Saito et al (1991) reported lethal and teratogenic effects in chick embryos following exposure to 428 MHz RF radiation at a power density of 5.5 mW/cm². The low level radiation was applied throughout most of the incubation period over 20 days. The authors justify their use of chick embryos in preference to mammals on the basis that temperature was controlled and SAR was accurately estimated. Whereas, in rodents the body temperature fluctuates considerably with metabolic activity and the maternal animals move about in the RF field causing substantial variations in their SAR. Delayed embryonic development was demonstrated by the incubation period being prolonged by approximately 1 day in the exposed group. Lethal effects were found in 60% of the exposed group where SAR ranged from 3.1 to 47.1 mW/kg depending on the position of the egg in the field. By comparison, deaths in the control group amounted to 16%. The authors report these effects as evidence of non-thermal effects of RF radiation. They speculated that RF radiation interferes with cell-cell interaction during embryonic cell development and migration. These authors have also reported adverse biological effects in mice from low intensity RF radiation at 433 and 906 MHz (Japanese language paper). Effects included reduced weight of the thymus in offspring of irradiated mothers and prolonged gestation.

In a follow-up study, Saito and Suzuki (1993 Japanese Teratology Society Conference) reported retarded development measured as a reduction in somite number in chick embryos following exposure to the same SAR levels of RF radiation at 428 MHz. In this study embryos were exposed for 48 hours and examined immediately afterwards. Somite counting is a standardised method of quantifying development in vertebrate embryogenesis. It was concluded that gene expression in early embryogenesis had been disturbed by a non-thermal mechanism. The evidence for this claim will, presumably, be stated in the published paper.

Most modern studies, particularly at ELF frequencies, are carefully designed to avoid unwanted exposure (and potential cellular responses) from ambient power line electromagnetic fields. Specially shielded incubators are custom built for cell culture exposure systems. It is not certain that this fastidious approach is applied to the teratogenic RF studies. The initiation of subtle cell responses (e.g. involving alteration of intracellular calcium ion concentration) appears to depend on an ELF component in the exposure. It is, therefore, possible that the effects of RF and microwave radiation may be potentiated by the presence of an ELF field generated by heaters, transformers and electric fans in commercial incubators. Indeed, the authors may be correct in their assessment that the observed adverse effects on development are due to interference of the cell-cell interaction and migrations. Nevertheless, the reported effect is important. The potential for a synergistic effect between ELF and RF exposures in embryonic and fetal development needs to be further investigated.

Reference has been made in the media to a report from Germany (Telecom Europa 1993, refer to chapter on media headlines) of lethal effects in chick embryos from exposure to radiation from cellular telephones. It has been impossible to obtain any publications or information on this matter from the original source. It is assumed that the media article was originally prepared from a verbal presentation. In the absence of a published paper no further comment can be made at this time.

Results from Marcickiewicz et al (1986) suggest a synergistic association of teratogenic drugs and high intensity RF exposures.